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Original Article

Early Detection of Subclinical Atherosclerosis in Asymptomatic Patients Assessed by Carotid Duplex and Coronary Computed Tomography☆

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SUMMARY

Background: The objective of this study is to determine the presence of early-stage atherosclerosis and the determinants of those with abnormal intima-media thickness (IMT) without coronary calcification assessed by carotid duplex and coronary computed tomography in a relatively healthy population and to compare the results from the two detection methods.

Materials and methods: Data of 181 asymptomatic participants [mean age 50.8 (35–72) years, 131 males] regarding baseline characteristics; blood biochemistries; Framingham risk score (FRS); metabolic score (MS); either carotid intima-media thickness (CIMT) or plaque, or both; and coronary artery calcification score (CACS) were obtained. Distributional differences between categorized atherosclerosis groups defined by various methods were compared using Chi-square test, while uni- and multivariate analyses were conducted to establish independent risk of atherosclerosis.

Results: For all participants, the mean MS was 1.58 and mean FRS was 5.99. Zero CACS was found in 123 individuals, of whom 75 (61%) had abnormal CIMT or plaque existence. After adjusting the confounders, both male gender and larger BMI were found to be significantly associated with abnormal CIMT or plaque existence in patients with zero CACS in multivariable regression model.

Conclusion: Carotid duplex may detect subclinical vascular atherosclerosis in more than half of asymptomatic patients without coronary artery calcification detected by coronary computed tomography. These findings have important implications for early-stage atherosclerosis screening and implementation of primary preventive intervention.

1. Introduction

Atherosclerotic cardiovascular disease (CVD) results in more than 19 million deaths worldwide annually, and coronary artery disease (CAD) may account for the majority of this toll[1,2]. Despite major treatment advances in patients with CAD, there are still victims suffering from sudden cardiac death who are apparently healthy without prior clinical symptoms. In this regard, early identification of the "vulnerable" patient population could be clinically important because sudden death as the initial manifestation was observed in up to 20% of the whole CAD population[3] and the prognosis of these survivors was generally poor[4–6].

So far, it remains clinically challenging to identify those who would most benefit from the delivery of primary preventive therapeutics beyond lifestyle modifications. Conventional cardiovascular risk stratification scoring, such as the Framingham risk score (FRS) and metabolic risk score (NCEP-ATP III score)[7,8], is effective in assigning risk for a large population, although is limited in the ability to characterize individual risk[9–11]. Noninvasive screenings tools, including coronary artery calcium score (CACS) by multidetector computed tomography (MDCT) and carotid intima-media thickness (CIMT) by duplex methods, are both well-described, effective measures that can be introduced to identify early-stage atherosclerosis with consensus panels established and recommended as potential additional risk stratifiers for CVDs[12–14].

☆ All contributing authors declare no conflicts of interest.

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Although both CIMT and CACS can detect subclinical atherosclerosis, the correlation between these two measures has been reported to be relatively weak, partly because of their baseline differences in disease nature and ethnicity, and because coronary calcification may actually reflect a more advanced stage of vascular diseases[13,15,16]. Taken together, for patients with more early-stage atherosclerosis characterized by increased CIMT or plaque formation using carotid duplex examination, yet without coronary artery calcification, namely "zero CACS", may still worth earlier therapeutic intervention. Therefore, the aim of this study was to examine the differences and characters of atherosclerosis defined by carotid duplex and MDCT methods in a cohort of asymptomatic adults seeking CVD survey.

2. Materials and methods

We enrolled 181 asymptomatic participants (mean age: 50.8 years; range: 35–72 years) without known CVDs who had at least one CVD risk (including smoking, hypertension, diabetes, hyperlipidemia, or family history of premature CVD) from January 1, 2006 to December 31, 2008. Both MDCT and carotid duplex were performed as screening tools for identifying subclinical atherosclerosis. Participants were excluded if they were noticed to have poorly controlled diabetes (HbA1c $>$ 9.0%) or severe hypertension ($>$180 mmHg for systolic or $>$120 mmHg for diastolic blood pressure), or were currently undergoing hemodialysis. All participants had detailed medical and family history reviewed through structured questionnaire. Baseline anthropometric data and physical examination records were collected and analyzed. Biochemical data, including fasting and postprandial serum glucose, lipid profiles, blood urea nitrogen, and creatinine level, were all obtained by Hitachi 7170 Automatic Analyzer (Hitachi Corp., Hitachinaka, Ibaraki, Japan). Participants were further stratified into low, intermediate, and high FRS with assignment of different metabolic score (MS) categories based on baseline demographic data, anthropometrics, and biochemical data[17].

2.1. CACS quantification

Detection and computation of coronary artery calcification were performed using a dedicated offline workstation (Aquarius 3D Workstation, TeraRecon, San Mateo, CA, USA) by an automated, electron-beam CT method. A coronary calcified lesion was defined as an area with a density $>$130 HU and covering at least six pixels by a CT scout image. The Agaston score method was applied by multiplying each lesion (area) by a weighted CT attenuation score in the lesion assessment.

2.2. CIMT measurement

The extracranial carotid arteries were assessed with high-resolution ultrasound scanners, either Acuson Aspen (Acuson Aspen, Siemens, Malvern, Pennsylvania) or Logiq 7 (GE Healthcare, Milwaukee, WI, USA), equipped with a 7.5–10 MHz linear-array transducer. Carotid images were obtained by a trained and certified vascular technologist. Ultrasonography evaluations were performed in a room with a comfortable temperature following 5–10 minutes of resting in the supine position. Using a leading edge-to-leading edge technique, all participants had an IMT measurement at the far wall of the distal 1 cm of each common carotid artery (CCA), carotid bulb, and proximal 1 cm of each internal carotid artery (ICA). IMT was defined, according to the Mannheim consensus criteria, as a double-line pattern visualized by B-mode imaging on both walls of the carotid arteries in a longitudinal image. In the evaluation of the presence or absence of carotid plaques, full extracranial arterial bed was interrogated using both transverse and longitudinal views. Carotid plaque was defined as

Table 1
Characteristics of baseline demographic data, serum biochemistries and estimated cardiovascular risk scores categorized by subclinical atherosclerosis in this study.

	No coronary calcification		All	Coronary calcification		All	p
	$n = 123$			$n = 58$			
	Normal IMT	Abnormal IMT or plaque		Normal IMT	Abnormal IMT or plaque		
	$n = 48$	$n = 75$		$n = 15$	$n = 43$		
Age (y)	48.5 ± 6.4	49.8 ± 6.7	49.3 ± 6.6	51.7 ± 3.6	54.9 ± 6.6	54.1 ± 6.1	<0.0001
Sex, male (%)	18 (22.5)	62 (77.5)*	80 (61)	12 (23.5)	39 (76.5)	51 (38.9)	0.001
SBP (mmHg)	110 ± 13.1	122.6 ± 14.3*	117.6 ± 15.1	120.9 ± 13	127.7 ± 14.9	126 ± 14.6	0.0006
DBP (mmHg)	70.8 ± 10.5	78.3 ± 9.7*	75.4 ± 10.6	74 ± 6.8	78.4 ± 10.2	77.3 ± 9.6	0.25
Waist (cm)	74.7 ± 8.2	85 ± 7.7*	81 ± 9.3	82.2 ± 6.5	86.2 ± 7.5	85.2 ± 7.4	0.003
Waist–hip ratio	0.83 ± 0.07	0.91 ± 0.06*	0.88 ± 0.07	0.89 ± 0.04	0.92 ± 0.05	0.91 ± 0.05	0.003
BMI (kg/m^2)	21.8 ± 2.6	24.9 ± 2.7*	23.7 ± 3	23.3 ± 2.7	24.8 ± 2.5	24.4 ± 2.6	0.13
AC sugar (mg/dL)	92.3 ± 9.4	102.4 ± 23.4*	98.5 ± 19.8	97.4 ± 12.4	105.1 ± 18.3	103.1 ± 17.2	0.13
PC sugar (mg/dL)	102.4 ± 18.4	108.6 ± 35.5	106.1 ± 30.1	103.6 ± 19.9	131.3 ± 54.4	123.9 ± 49.1	0.004
Cholesterol (mg/dL)	199 ± 39.1	200.5 ± 37.6	199.9 ± 38	183.7 ± 29.2	197.3 ± 29	193.7 ± 29.4	0.28
Triglyceride (mg/dL)	103.5 ± 55.7	149.1 ± 75.6*	131.2 ± 71.8	113.1 ± 82.9	144.2 ± 77.5	136.1 ± 79.4	0.68
LDL (mg/dL)	126 ± 37.4	132.3 ± 33.4	129.8 ± 35.1	121.1 ± 26.5	129.5 ± 30.2	127.2 ± 29.2	0.64
HDL (mg/dL)	62.9 ± 13.8	50.9 ± 12.7*	55.7 ± 14.3	50.2 ± 9.2	48.1 ± 13.8	48.7 ± 12.7	0.002
Uric acid (mg/dL)	5 ± 1.4	5.9 ± 1.2*	5.5 ± 1.3	5.2 ± 1.4	6 ± 1.3*	5.8 ± 1.4	0.20
eGFR (mL/min/1.73 m^2)	88 ± 17	85.7 ± 14.3	86.6 ± 15.4	88.3 ± 11.8	81.7 ± 16.5	83.4 ± 15.5	0.21
Metabolic score, mean (median, 25th–75th)	0.4 (0, 0–1)	1.9 (2, 1–3)*	1.3 (0, 0–2)	1.6 (1, 0–3)	2.3 (2, 1–3)	2.1 (2.5, 1–4)	0.0004
Framingham score, mean (median, 25th–75th)	2.7 (2, 1–4)	6.1 (5, 2–8)*	4.8 (4, 1–8)	5.4 (7, 3–8)	9.1 (8, 5–13)*	8.2 (7.5, 5–11)	<0.0001
Hypertension (%)	7 (14.6)	36 (48)*	43 (35)	7 (46.7)	20 (46.5)	27 (46.6)	0.14
Diabetes (%)	6 (12.5)	19 (25.3)	25 (20.3)	6 (40)	15 (35)	21 (36.2)	0.02
Exercise (yes) (%)	7 (14.6)	9 (12)	16 (13)	4 (26.7)	9 (20.9)*	13 (22.4)	0.84
Smoking, current (yes) (%)	4 (23.5)	13 (76.5)	17 (65.4)	2 (22.2)	7 (77.8)	9 (34.6)	0.71

*$p < 0.05$ when compared to normal IMT group.
p: All (no coronary calcification group) versus All (coronary calcification group).
Hypertension was defined as SBP ≥140 mmHg or DBP ≥90 mmHg; diabetes was defined as AC sugar >126 mg/dL, PC sugar >200 mg/dL.
AC sugar = fasting glucose; BMI = body mass index; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; IMT = intima-media thickness; LDL = low-density lipoprotein; PC sugar = postprandial glucose; SBP = systolic blood pressure.

the presence of focal wall thickening that is at least 50% greater than that of the surrounding vessel wall or as a focal region with CIMT greater than 1.5 mm that protrudes into the lumen that is distinct from the adjacent boundary. All measurements were repeated three times, and the mean value was noted.

Based on a previous epidemiologic Taiwanese population study, an average of right and left common CIMT was used as the representative CIMT, as reported previously[18]. Patients with abnormally high average CIMT (>0.68 mm) or presence of plaque on CCA, ICA, external carotid artery, bulb, or bifurcation were defined as having carotid atherosclerosis.

2.3. Traditional cardiovascular risk scores

Traditional cardiovascular risk scores including MS and FRS were calculated. MS was presented as the numbers of abnormal components meeting the National Cholesterol Education Program (NCEP) Panel III criteria (ATP III), with score 0 representing absence of any abnormal metabolic items and 5 representing an individual with all five abnormal metabolic items. The calculation of FRS was assessed as previously described[19,20].

2.4. Statistical analysis

Continuous data were expressed as mean ± standard deviation, and categorical data were expressed as frequency or proportion. Differences of baseline demographics between groups were tested by Student *t* test or Mann–Whitney *U* test, with categorical data being analyzed by Chi-square or Fisher exact test as appropriate. As mentioned before, patients with any abnormal carotid findings, including existence of plaque or abnormally high mean CIMT (≥0.68 mm), were defined as subclinical atherosclerosis by carotid duplex method[18]. Patients with detected coronary calcium deposition presented as a CACS larger than zero were classified as having subclinical atherosclerosis, as detected by MDCT. Various combinations of abnormal carotid scan results (by either CIMT or existence of plaque or not) were further categorized into different groups and compared with coronary calcium deposition by using Chi-square test to see whether there remained a significant distribution between these two different modalities in assessing subclinical atherosclerosis. Uni- and multivariate logistic regression models were used to determine the baseline clinical variables, anthropometrics, or related biochemical data in the prediction of

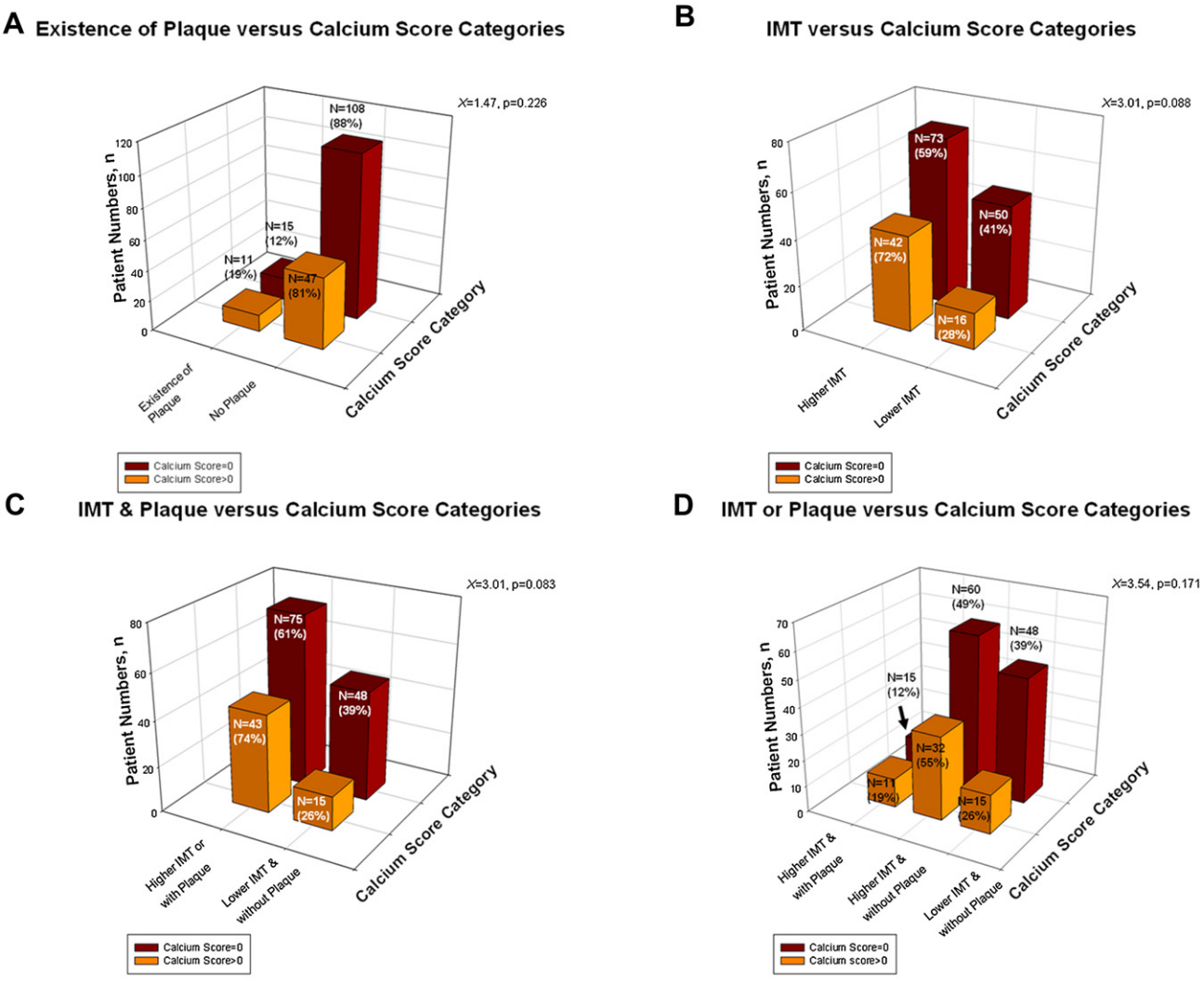

Fig. 1. Various combinations of carotid scan results based on IMT or existence of plaque or not in relation to coronary artery calcium deposition were displayed and compared by using Chi-square test. (A) Existence of plaque or not; (B) abnormal IMT or not by 0.68 mm cutoff; (C) either abnormal IMT or existence of plaque versus those without any abnormal findings; and (D) normal IMT without plaque versus those including abnormal IMT with or without plaque, respectively. These different combinations of carotid scan results failed to categorize successfully abnormal carotid scan results into significant distributional differences in relation to coronary calcium deposition. IMT = intima-media thickness.

plaque existence or abnormally high CIMT with individual odds ratio (OR), significance (p), and 95% confidence interval (95% CI) reported.

STATA 8.2 (Stata Corp., College Station, TX, USA) and SPSS 11.0 (SPSS Inc., Chicago, IL, USA) were used to perform statistical analyses, and the significance of p level (α-value) was two sided and set as 0.05.

3. Results

3.1. Baseline clinical information

Table 1 lists the baseline information, anthropometrics, and both estimated cardiovascular risk scores based on the presence of coronary calcification with or without subclinical atherosclerosis by carotid duplex scan in our study. Of 181 patients (mean age: 50.8 ± 6.8 years, female: 28%), 123 (68%) had zero CACS while 58 had coronary calcification (Fig. 1). For those 123 patients without obvious coronary calcification, 75 (61%) had subclinical atherosclerosis detected by carotid duplex, while for those with obvious coronary calcification, up to 74% ($n = 43$) had carotid anomaly defined by CIMT thickness or existence of plaque (Fig. 1). Generally, older age, gender, higher blood pressure, and unfavorable anthropometrics (waist and waist−hip ratio) were found in the coronary calcification group when compared to those without coronary calcification ($p < 0.05$), regardless of the carotid findings. Also, higher postprandial serum sugar and lower high-density lipoprotein (HDL) level were noted in those with coronary calcification ($p < 0.05$), together with a higher FRS and MS (mean FRS: 8.2 vs. 4.8, $p < 0.0001$, and mean MS: 2.1 vs. 1.3, $p = 0.0004$, respectively). Distributions of various combinations of abnormal carotid scan results (when categorized individually by CIMT anomaly or the existence of plaque or not) related to coronary artery calcium deposition (with or without) were further illustrated in Figs. 1 and 2. In brief, whether the coronary calcium deposition existed or not did not seem to classify successfully various combinations of abnormal carotid scan results in binary groups (Fig. 1: all Chi-square result >0.05), and the calcium scores are persistently higher for patients with low CIMT in the absence of carotid plaque when compared to those groups with abnormal CIMT and/or presence of carotid plaque (Fig. 2, groups C and D).

In the group without coronary calcification, those with abnormal carotid findings ($n = 75$) had similarly unfavorable anthropometrics (waist and waist−hip ratio), lipid profiles, both higher estimated cardiovascular risks and higher prevalence of hypertension, diabetes, and smoking behavior. However, these differences between normal and abnormal carotid scans were less significant in the group with coronary calcification.

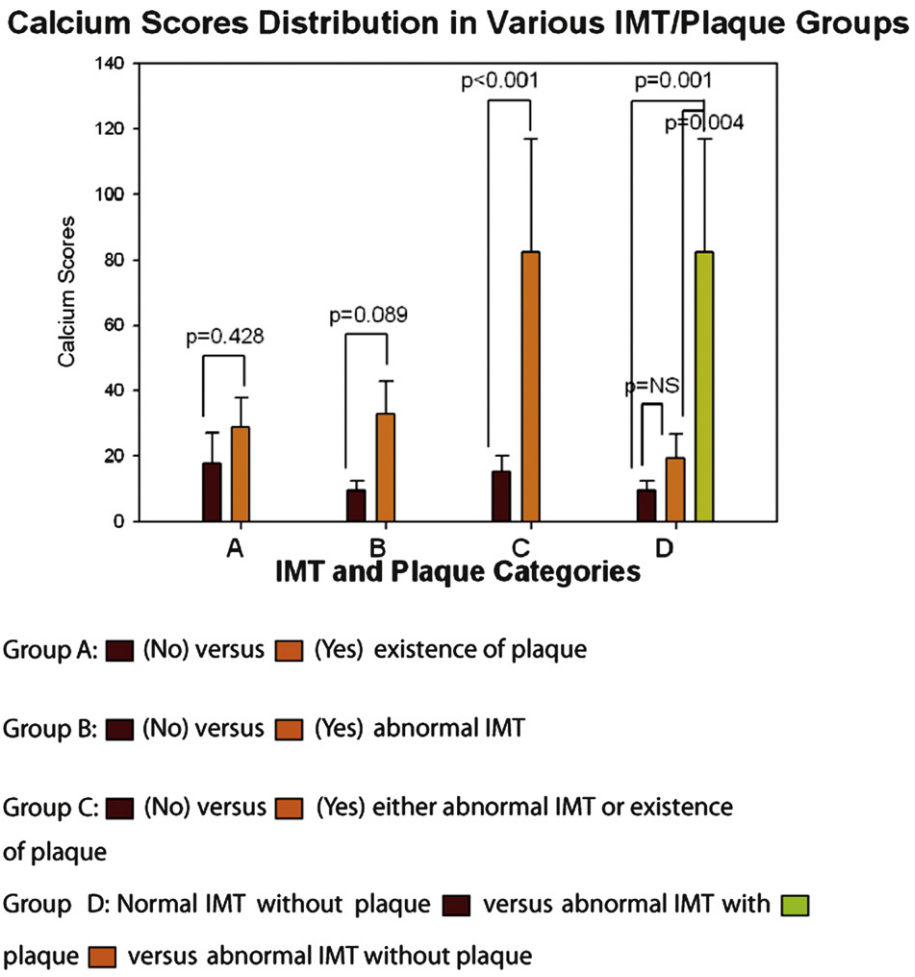

Fig. 2. Various combinations of carotid scan results based on IMT or existence of plaque or not in relation to coronary calcium scores were further displayed. (A) Existence of plaque or not; (B) abnormal IMT by 0.68 mm cutoff; (C) either abnormal IMT or existence of plaque; and (D) normal IMT without plaque and those including abnormal IMT with or without plaque, respectively. For those with either abnormal IMT or existence of plaque (C) and those with abnormal IMT together with plaque (D) have significantly larger coronary calcium scores when compared to the other category in each group. IMT = intima-media thickness.

Table 2
Data of different IMT measures and the association with coronary calcium deposition.

	No coronary calcification		All (mean)	Coronary calcification		All (mean)	*p*
	$n = 123$			$n = 58$			
	Normal IMT	Abnormal IMT or plaque		Normal IMT	Abnormal IMT or plaque		
	$n = 48$	$n = 75$		$n = 15$	$n = 43$		
Rt CCA (mm), mean (50th, 25th–75th)	0.65 (0.65, 0.63–0.68)	0.74 (0.74, 0.69–0.78)*	0.70 ± 0.07	0.65 (0.66, 0.62–0.68)	0.76 (0.75, 0.70–0.79)*	0.73 ± 0.08	0.04
Lt CCA (mm), mean (50th, 25th–75th)	0.63 (0.63, 0.62–0.65)	0.73 (0.73, 0.69–0.76)*	0.69 ± 0.07	0.63 (0.61, 0.59–0.67)	0.74 (0.73, 0.69–0.78)*	0.71 ± 0.08	0.08
Rt Bif (mm), mean (50th, 25th–75th)	0.86 (0.85, 0.78–0.95)	0.95 (0.95, 0.87–1.03)*	0.91 ± 0.12	0.90 (0.9, 0.8–0.98)	1.00 (0.98, 0.93–1.06)*	0.97 ± 0.11	0.002
Lt Bif (mm), mean (50th, 25th–75th)	0.87 (0.87, 0.83–0.92)	0.96 (0.94, 0.89–1.04)*	0.93 ± 0.11	0.89 (0.84, 0.78–1.0)	0.99 (0.99, 0.9–1.07)*	0.96 ± 0.12	0.06
Plaque, numbers	0	15	15	0	11	11	0.23

*p <0.05 when compared to normal IMT group.
p: All (no coronary calcification group) versus All (coronary calcification group).
Bif = bifurcation; CCA = common carotid artery; IMT = intima-media thickness; Lt = left; Rt = right.

3.2. Carotid findings associated with coronary calcification

In Table 2, we have further listed the detailed information of carotid duplex scan in those with and without coronary calcification. The mean IMT values between normal and abnormal carotid scan groups categorized by the existence of coronary calcification were also displayed. We observed that several carotid abnormal characters in terms of higher CIMT thickness (for right CCA and right bifurcation, $p = 0.04$ and $p = 0.002$, respectively) were observed in those who developed coronary calcification when compared to those who did not. Also, we observed a borderline increase of IMT at right common and left bifurcation carotid artery area in those with coronary calcification when compared to those without ($p = 0.08$ and $p = 0.06$, respectively). However, the distributional proportion of carotid plaque existence between two different coronary groups was not different ($p = 0.23$).

3.3. Association between traditional cardiovascular risks and carotid duplex findings

Abnormal carotid duplex findings including existence of plaque or abnormally high IMT in relation to traditional estimated cardiovascular risks (MS and FRS) are listed in Table 3. Consistently higher IMT in the abnormal MS score group (≥3) compared with the normal MS group (all $p < 0.05$) was observed in all participants as well as in those with coronary calcium score equal to zero. In addition, abnormal MS was significantly associated with higher proportion of abnormal carotid scan result, regardless of the types of combination, except for existence of plaques that did not reach statistical significance.

For all participants and those with CACS of zero, intermediate- to high-risk population, based on FRS, was associated with higher IMT and all abnormal carotid scan results, except for

Table 3
Distribution of abnormal carotid scan results based on different estimated cardiovascular scores from all and those with zero CACS.

	Estimated cardiovascular risk scores	Group 1	Group 2	*t* Test	*p* for Chi-square or Fisher exact test
	Metabolic score (0–5)	0 (normal MS)	≥3 (abnormal MS)		
All ($n = 181$)		$n = 135$	$n = 46$		
	IMT (mm)	0.69 ± 0.07	0.73 ± 0.07	0.001	—
	Plaques (%)	15 (11.4)	11 (22.5)	—	Chi = 3.57, $p = 0.06$
	Higher IMT and no plaque (%)	60 (45.5)	32 (65.3)	—	Chi = 5.63, $p = 0.02$
	Plaques or higher IMT (%)	75 (56.8)	43 (87.8)	—	Chi = 15.07, $p < 0.001$
	Plaques and higher IMT (%)	12 (9.1)	11 (22.5)	—	Chi = 5.75, $p = 0.02$
Coronary calcium score = 0 ($n = 123$)		$n = 90$	$n = 33$		
	IMT (mm)	0.69 ± 0.06	0.74 ± 0.06	0.0006	—
	Plaques (%)	9 (9.4)	5 (21.7)	—	Chi = 2.73, $p = 0.010$
	Higher IMT and no plaque (%)	42 (43.8)	17 (73.9)	—	Chi = 6.75, $p = 0.009$
	Plaques or higher IMT (%)	51 (53.1)	22 (95.7)	—	Chi = 14.15, $p < 0.001$
	Plaques and higher IMT (%)	7 (7.3)	5 (21.7)	—	Chi = 4.27, $p = 0.04$
	Estimated cardiovascular risk scores	Group 1	Group 2		
	Estimated cardiovascular risk scores	Group 1	Group 2	*t* Test	*p* for Chi-square or Fisher exact test
	Framingham risk score (5, 20)	Low risk (≤5)	Intermediate to high risk (6–20)		
All ($n = 181$)		$n = 106$	$n = 75$		
	IMT (mm)	0.7 ± 0.07	0.75 ± 0.06	<0.0001	—
	Plaques (%)	16 (10.4)	10 (37)	—	chi = 13.26, p<0.0001
	Higher IMT and no plaque (%)	75 (48.7)	17 (63)	—	chi = 1.87, p = 0.17
	Plaques or higher IMT (%)	91 (59.1)	27 (100)	—	chi = 16.94, p<0.0001
	Plaques and higher IMT (%)	14 (9.1)	9 (33.3)	—	chi = 12.17, p<0.0001
Coronary calcium score = 0 ($n = 123$)		N = 81	N = 42		
	IMT (mm)	0.69 ± 0.06	0.78 ± 0.07	<0.0001	—
	Plaques (%)	10 (9.2)	4 (40)	—	Chi = 8.38, $p = 0.02$
	Higher IMT and no plaque (%)	53 (48.6)	6 (60)	—	Chi = 0.47, $p = 0.49$
	Plaques or higher IMT (%)	63 (57.8)	10 (100)	—	Chi = 6.88, $p = 0.009$
	Plaques and higher IMT (%)	8 (7.3)	4 (40)	—	Chi = 10.78, $p = 0.001$

CACS = coronary artery calcium score; IMT = intima-media thickness; MS = metabolic score.

the combination of higher IMT without detectable carotid plaque.

3.4. Determinants of abnormal carotid duplex findings without coronary calcification

Uni- and multivariable models used in identifying the variables related to abnormal carotid findings defined as abnormally high IMT or existence of plaques are listed in Table 4. In the univariate model, male gender, increased blood pressure, higher body mass index or waist circumference, higher blood sugar, triglyceride and uric acid level, hypertension history, and both traditional cardiovascular risk factors all contributed significantly ($p < 0.05$) to increased risk of abnormal IMT or plaque development. In the different multivariable models, male gender and larger body mass index remained to be independent risk factors for abnormal carotid duplex findings even after adjustment for lipid profiles in patients without coronary artery calcium deposition.

Table 4
Odds ratio (95% CI and *p* value) for abnormal carotid IMT or plaque existence for zero CACS by uni- and multivariate analysis.

Univariate model	OR	95% CI	*p*
Existence of plaque or abnormally high IMT without coronary calcification			
Age (y)	1.03	0.98–1.09	0.27
Sex, male (%)	7.95	3.44–18.34	<0.0001
SBP (mmHg)	1.07	1.04–1.11	<0.0001
DBP (mmHg)	1.08	1.04–1.13	<0.0001
BMI (kg/m^2)	1.58	1.32–1.91	<0.0001
Waist (cm)	1.17	1.10–1.25	<0.0001
AC sugar (mg/dL)	1.09	1.04–1.15	0.001
PC sugar (mg/dL)	1.01	0.99–1.02	0.29
Cholesterol (mg/dL)	1.00	0.99–1.01	0.83
Triglyceride (mg/dL)	1.01	1.00–1.02	0.001
LDL (mg/dL)	1.00	0.99–1.02	0.34
HDL (mg/dL)	0.93	0.91–0.97	<0.0001
Uric acid (mg/dL)	1.79	1.31–2.45	<0.0001
eGFR (mL/min/1.73 cm^2)	0.99	0.97–1.01	0.43
Hypertension (%)	7.75	2.52–23.80	<0.0001
Diabetes (%)	2.75	0.85–8.86	0.09
Exercise_(yes vs. no)	0.95	0.31–2.88	0.93
Smoking (yes vs. no)	2.86	0.76–10.71	0.12
Metabolic score	3.99	2.31–0.69	<0.0001
Framingham score	1.29	1.13–1.47	<0.0001
Existence of plaque or abnormally high IMT without coronary calcification			
Model 1			
Age (y)	1.05	0.98–1.11	0.16
Sex	8.44	3.59–19.85	<0.0001
Model 2			
Age (y)	1.01	0.95–1.08	0.73
Sex	7.09	2.84–17.70	<0.0001
SBP (mmHg)	1.07	1.03–1.11	0.001
Model 3			
Age (y)	1.00	1.00–1.08	0.88
Sex	5.39	2.01–14.45	0.001
SBP (mmHg)	1.04	1.00–1.09	0.04
BMI (kg/m^2)	1.39	1.13–1.71	0.002
Model 4			
Age (y)	1.00	0.92–1.09	0.97
Sex	4.59	1.29–16.28	0.018
SBP (mmHg)	1.04	0.99–1.08	0.12
BMI (kg/m^2)	1.35	1.07–1.72	0.013
Hypertension	1.61	0.47–5.47	0.45
AC sugar (mg/dL)	1.01	0.95–1.07	0.82
Triglyceride (mg/dL)	1.01	0.99–1.02	0.55
Cholesterol (mg/dL)	0.97	0.87–1.09	0.65
HDL (mg/dL)	1.03	0.92–1.16	0.61
LDL (mg/dL)	1.02	0.91–1.15	0.72

Model 1: adjusted for age groups and gender.
Model 2 Model 1 plus systolic BP.
Model 3: Model 2 plus body mass index.
Model 4: Model 3 plus hypertension, fasting glucose, triglyceride, cholesterol, HDL, and LDL. AC sugar = fasting glucose; BMI = body mass index; CACS = coronary artery calcium score; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; IMT = intima-media thickness; LDL = low-density lipoprotein; PC sugar = postprandial glucose; SBP = systolic blood pressure.

4. Discussion

In this study, we reported the relationship between traditional cardiovascular risk scores and subclinical atherosclerosis in terms of both abnormal carotid artery study results and that defined by coronary artery calcification. We observed that there exists some discrepancy while using these different methods in defining the presence of atherosclerosis. We further explored the clinical determinants and different clinical manifestations for those with abnormal carotid duplex study results yet without coronary calcification deposits.

As previous studies have consistently shown that coronary calcification is an independent predictor of carotid artery atherosclerosis[21–23], data regarding the extent of possible abnormalities of carotid arteries without coronary calcification in asymptomatic patients remain scarce in Taiwanese population. The principal finding in this study is that a substantial percentage of relatively asymptomatic and healthy individuals free from coronary calcification may have subclinical atherosclerotic changes, as determined by ultrasonography study of the carotid arteries. The clinical significance of this finding is further emphasized by the well-established rule that atherosclerosis detected by ultrasonography of the carotid artery is a strong predictor of adverse cardiovascular events[24–27]. Similar results had been corroborated by investigators from Cedars-Sinai Medical Center, who found that 55% of a primary prevention population without coronary artery calcification or diseased thoracic aorta actually had carotid artery plaques as demonstrated by ultrasonography[28].

Although both carotid artery study and coronary artery calcium deposits may help risk stratification, their comparative abilities and potential diversity as screening tools in identifying early-stage, subclinical atherosclerosis in different populations remained less established. From our data, 48 (26.5%) patients who were classified as having low-risk carotid duplex study results also had low-risk CACS, and only 15 (8.29%) patients with low-risk carotid study results were placed into a higher-risk category because of abnormal coronary study, whereas 75 (41.4 %) patients with a CACS of zero had abnormal carotid study, which may indicate an even earlier-stage atherosclerosis. Furthermore, for those with abnormal carotid scan results, although having coronary calcium score of zero, also demonstrated higher cardiovascular risks scores in terms of either MS or FRS in our study. These findings further support the notion that carotid duplex study may be more useful than CACS for the detection of earlier-stage or subclinical atherosclerosis in asymptomatic patients. As CACS is helpful in determining whether or not a patient is at an increased risk of future adverse CVD events, these data may not be particularly clinically precise for asymptomatic patients with a CACS of zero. In this regard, carotid artery study may serve as a more useful measure of subclinical atherosclerosis with a higher negative predictive value in this group. Owing to the fact that implementation of carotid study results could be relatively simple and noninvasive for large-scale population studies, in our opinion, it is thus more suitable in clinical application.

From the viewpoint of preventive medicine, screening for CVD should not be limited to merely determining probability of a real diseased group; ideally, it should be able to detect early-stage or subclinical diseases. The results of this study indicated that carotid artery duplex could be more useful than CACS in detecting subclinical atherosclerosis in asymptomatic patients. In this

respect, early identification for earlier-stage atherosclerotic status by carotid artery study with effective therapeutic intervention provided would probably be most beneficial rather than clinical judgment by CT method, given the fact that arterial calcification may reflect as later stage of vascular diseases. More importantly, growing evidence also showed that its absence does not exclude the presence of noncalcified "vulnerable" plaque[29].

Accumulating data from clinical studies have readily shown that statins are able to slow the progression or even lead to carotid atherosclerosis regression by assessing CIMT via B-mode ultrasound measurement[30–32]. Although interventions have not been shown to be effective in reducing CACS, they have been shown to slow the progression of CIMT and even to result in partial regression[33]. Additionally, aggressive lipid lowering with atorvastatin has been shown to be more effective in reducing CIMT than conventional lipid-lowering therapy[34,35]. Therefore, carotid artery duplex may be a better alternative for monitoring disease progression during therapeutic interventions.

5. Limitations

First, the findings of this study are based on a relatively small sample size and are observational. However, large primary prevention trials involving patients with atherosclerosis as defined by CIMT will be both costly and lengthy.

Second, the definitive effect of an intervention was not tested in our study. However, the findings of METEOR trial demonstrate that in relatively same group of middle-aged adults with FRS lower than 10% and evidence of subclinical atherosclerosis, intervention of rosuvastatin treatment could result in statistically significant reductions in the rate of progression of maximum CIMT during a 2-year period compared with placebo.

6. Conclusion

Carotid duplex study is able to identify subclinical atherosclerosis in relatively healthy and asymptomatic patients with a CACS of zero. Even though the existence of abnormal CIMT without coronary calcium deposition still tracks with unfavorable cardiovascular risks by using conventional risk estimators. These findings may have important implications for vascular disease screening and implementation of primary prevention strategies in Taiwanese population.

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